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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,697	10/05/2006	Jurgen Wagner	33714-US-PCT	2925

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NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
WEBB, WALTER E	

ART UNIT	PAPER NUMBER
1609	

MAIL DATE	DELIVERY MODE
10/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,697	WAGNER ET AL.	
	Examiner	Art Unit	
	Walter E. Webb	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 12-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/05/2006 and 7/05/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-10 and 12-14 are pending and rejected.

Claim 11 has been cancelled.

Specification

Applicant is reminded of the proper content of an Abstract of the Disclosure.

In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class. For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example unless variations are necessary.

Complete revision of the content of the abstract is required on a separate sheet.

The abstract of the disclosure is objected to because there is no mention of the general nature of the compounds of formula I, II, III or IV, or how the compounds will be used in relation to transplantation and autoimmune diseases. Correction is required. See MPEP § 608.01(b).

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

The specification is objected to because it is not arranged according to 37 CFR 1.77(b). There are no section headings corresponding to the above arrangement e.g. the Title of the Invention, Background of the Invention, Brief Summary of the Invention, and Detailed Description of the Invention. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 and 12-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of transplant rejection, graft-versus-host disease, or an autoimmune disease, does not reasonably provide enablement for prevention of transplant rejection, graft-versus-host disease, or an autoimmune disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;

2) the breadth of the claims;

3) the predictability or unpredictability of the art;

4) the amount of direction or guidance presented;

5) the presence or absence of working examples;

6) the quantity of experimentation necessary;

7) the state of the prior art; and,

8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

Factors 1 and 2: The claimed invention is drawn a method and composition for treating or preventing organ transplant rejection, graft-versus-host disease, or an autoimmune disease.

Factors 3 and 7: In particular, one skilled in the art could not practice the presently claimed subject matter without undue experimentation because the artisan would not accept on its face that the prevention of transplant rejection, graft-versus-host disease, or an autoimmune disease, could be effectively achieved by the administration of the claimed active agent. Based on the state of the art, as discussed below, the artisan would have only accepted that the treatment of specific transplant rejection, graft-versus-host disease, or an autoimmune disease could be achieved, rather than that such an agent could have been used to prevent these diseases.

As set forth in *In re Marzocchi* et al., 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains teaching of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112 unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support; assuming that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling."

Factor 4: Applicant disclosed guidance in the form of animal studies showing that the composition maintained a rejection-free state in animals after heart transplantation. To enable the artisan to reasonably predict that Applicant's composition can prevent transplant rejection, graft-versus-host disease, or an autoimmune disease, Applicant should set forth stronger evidence. Applicant's disclosure is inadequate as to directing or guiding how the proposed agents can be employed to accomplish such objectives in a predictable manner.

Factor 5: The specification at pages 11-14 provides evidence demonstrating that the composition maintained a rejection-free state in animals after heart transplantation, and treatment of multiple sclerosis (MS) in a mouse model. While the present claims encompass preventing transplant rejection, or immune-mediated and/or inflammatory disease, Applicant's data merely establishes treatment of MS in a mouse and maintenance of a rejection free state with continuous administration of the composition. No data has been provided, or reasonable scientific basis exists, for treating such results as a prevention of transplant rejection, graft-versus-host disease, or an autoimmune disease.

For example, treatment of Diabetes Mellitus, an autoimmune disease, is well developed (see Merck Manuel, Diabetes Mellitus (DM): Diabetes Mellitus and Disorders of Carbohydrate Metabolism, http://www.merck.com/mmpe/sec12/ch158/ch158b.html.), but the state of the art with regard to preventing this disease, in general, is grossly underdeveloped.

In this regard, The Merck Manuel is cited. In particular, there is no known agent that is effective against preventing Diabetes Mellitus. The Merck reference clearly shows that for the different symptoms associated with Diabetes Mellitus and the severity of the disease, there is not one agent or combination thereof that is effective at preventing every symptom (see Insulin regimens for type 1 DM at pg. 14, Oral Antihyperplycemics at pp. 15-17, and Prevention at pp. 21-21.).

In another example, treatment of transplant rejection is also well developed (See Prescilla et al., Immunology of Transplant Rejection, eMedicine at http://www.emedicine.com/ped/topic2841.htm.), but the state of the art with regard to preventing this disease, in general is underdeveloped.

In this regard, Prescilla et al. is cited. There is no known agent that is effective against all forms of rejection. Prescilla et al. clearly show that there is not one agent or therapeutic strategies for treating rejection in general. (see Rejection, sec. 7 at pg. 4) They state, in fact, that there is no accepted therapeutic strategy for chronic rejection. (See ibid.)

Given that there was no known specific agent or combination of agents effective to prevent Diabetes Mellitus or transplant rejection, one of ordinary skill in the art would not accept on its face Applicant's statement that such an objective could be achieved with transplant rejection, graft-versus-host disease, or an autoimmune disease. The artisan would have required sufficient direction as to how to predict what particular type of transplant rejection, graft-versus-host disease, or autoimmune disease would actually show sensitivity to the presently claimed composition such that the artisan would have

been imbued with at least a reasonable expectation of success in preventing such diseases. Such success would not have been reasonably expected for preventing transplant rejection, graft-versus-host disease, or an autoimmune disease given the variable nature of transplant rejection, or Diabetes Mellitus known in the art. The prevention of symptoms associated with Diabetes Mellitus or chronic rejection, for example, would have been an outcome not reasonably expected by one of ordinary skill in the art. To the artisan, the concept of a single agent, or even a combination of agents, that is effective to prevent transplant rejection, graft-versus-host disease, or an autoimmune disease would have been unique and, thus, met with a great deal of skepticism.

The Examiner acknowledges that the Office does not require the presence of working examples to be present in the disclosure of the invention (see MPEP §2164.02). However, in light of the state of the art, which recognizes the unpredictable nature of preventing Diabetes and transplant rejection, there is no apparent disclosure to support the contention that transplant rejection, graft-versus-host disease, or an autoimmune disease can be prevented by simply administering, by any method, the claimed composition, since the present specification fails to enable one of ordinary skill in the art to practice the entirety of the presently claimed invention.

Factor 6: The burden of preventing transplant rejection, graft-versus-host disease, or an autoimmune disease with the claimed composition is much greater than that of treating transplant rejection, graft-versus-host disease, or an autoimmune disease, with the claimed composition. Since the present specification would not enable

one of ordinary skill in the art to prevent transplant rejection, graft-versus-host disease, or an autoimmune disease with the claimed composition, a clear burden of undue experimentation would be placed upon one of ordinary skill in the art in order to practice the full scope of the presently claimed invention.

Factor 8: In view of the discussion of each of the preceding seven factors, the level of skill in this art is high and is at least that of a medical doctor with several years of experience in the art.

Summary

As the discussion of the above 8 factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue one of ordinary skill in the art with a reasonable expectation that preventing transplant rejection, graft-versus-host disease, or an autoimmune disease with the claimed composition could be achieved. In order to actually achieve such an objective, it is clear from the discussion above that one of ordinary skill in the art could not rely on Applicant's disclosure as required by 35 U.S.C. § 112, first paragraph. Given that the art fails to recognize, and Applicant has failed to demonstrate, via direct evidence or sound reasoning, that transplant rejection, graft-versus-host disease, or an autoimmune disease can be prevented with the claimed composition, one of ordinary skill in the art would be faced with the impermissible burden of undue experimentation in order to practice this embodiment of the claimed invention. Accordingly, claims 1-10 and 12-14 are deemed properly rejected.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-8, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Heath et al., (US 5,545,636).

Applicant's invention is drawn to a method for treating or preventing organ or tissue transplant rejection or an autoimmune disease or for preventing graft versus host disease by administering a protein kinase C inhibitor of formula I, II, III, or IV (claim 1, 3-5, and 13). Applicant also claims a composition of formula I, II, III, or IV (claims 6 and 7), where the compound can be 3-(1-methyl-1H-indol-3-yl)-4-[1-(piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione (claim 8).

Heath et al. teach a protein kinase C inhibitor of formula I, II, III, and IV with every limitation therein. (See col. 2 lines 50-64, col. 3 lines 1-32, and lines 40-65, col. 4 lines 1-25, and lines 26-56, and lines 60-65, and col. 5 lines 1-23.) The compound 3-(1-methyl-1H-indol-3-yl)-4-[1-(piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione is taught at col. 53, Example 68, lines 19-32, as being one of those inhibitors. They teach a method of treating diabetes mellitus by administering to a mammal in need their protein kinase C inhibitors. (See col. 11, lines 60-66; see also col. 62, lines 12-14 the claims.) It is well known that diabetes mellitus is an autoimmune disease, as per the claims. (See, Bach in particular, pg. 523 sec. V, right column.)

Note that all claims encompass "preventing," which reads on anyone since anyone can benefit or be in need of preventing anything.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10 and 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heath et al. (*supra*) as applied to claims 1, 3-8, and 13 above, and in further view of Albert et al., (US 2004/0053949).

Applicant claims a method according to claim 1 where the autoimmune disease can be rheumatoid arthritis (claim 2 and 12) and a composition that includes at least

one second agent selected from an immunosuppressant and immunomodulatory drug (claims 9, 10, and 14).

Heath et al. teach a protein kinase C inhibitor of formula I, II, III, and IV with every limitation therein. (See col. 2 lines 50-64, col. 3 lines 1-32, and lines 40-65, col. 4 lines 1-25, and lines 26-56, and lines 60-65, and col. 5 lines 1-23.) The compound 3-(1-methyl-1H-indol-3-yl)-4-[1-(piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione is taught at col. 53, Example 68, lines 19-32.

Heath et al. does not teach where the autoimmune disease can be rheumatoid arthritis or a composition that includes at least one second agent selected from an immunosuppressant and immunomodulatory drug.

Albert et al. teach protein kinase C inhibitors (see page 18 para. [0221]), that can be administered with an immunomodulatory drug (see page 20 para. [0255]). They also teach that protein kinase C inhibitors are useful in treating many diseases including rheumatoid arthritis (see page 19 para. [0245].)

It would have been obvious to a person of ordinary skill in the art at the time of applicant's invention to combine the compound of Heath with an immunomodulatory compound and to use the compound of Heath to treat rheumatoid arthritis, since Albert teaches that combining an immunomodulatory compound with a protein kinase C inhibitors further aids in the treatment of autoimmune diseases, and inhibition of protein kinase treats rheumatoid arthritis. Heath et al. teach that protein kinase C inhibitors have been shown to block inflammatory responses (see col. 12, lines 1-5). Therefore,

one of ordinary skill in the art would know that the compound of Heath could have been used to treat rheumatoid arthritis, since it is an inflammatory disease.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Walter E. Webb whose telephone number is (571) 270-3287. The examiner can normally be reached on 9:00am-5:00pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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JEFFREY STUCKER
SUPERVISORY PATENT EXAMINER